--98. The dry powder inhaler device of claim 78, wherein the pharmaceutical composition is non-hygroscopic.--

--99. The composition of claim 61, wherein the composition is non-hygroscopic.--

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--100. The method of claim 21, wherein the composition is non-hygroscopic.--

REMARKS

The title and abstract (Appendix A) of the application have been amended to more clearly indicate the invention to which the claims are directed, as requested by the Examiner at Section 10, page 4 of the Office Action.

Claims 1-16, 21, 22, 26-32, and 50-100 are now pending in the present application, claims 17-20 and 33-49 having been cancelled and claims 61-100 added by the above amendment. Claim 1 has been amended, and new claims 98-100 added, to limit the dry powder to a non-hygroscopic dry powder. Support for this limitation can be found in the specification at page 14, lines 25-32, as well as at page 12, lines 16-19. Claim 21 has been amended to limit the administration to inhalation through the mouth, support for which can be found in the specification at page 2, lines 1-3; page 6, line 4; page 14, lines 21-25; and page 18, lines 23-27. New claims 61-77 are directed to pharmaceutical compositions containing particles of a pharmaceutically acceptable carrier so as to create an ordered

mixture, support for which can be found in claims 1-16, 31, and 32. New claims 78-98 are directed to a dry powder inhaler device containing a composition of the invention, support for which can be found in original claims 1-19, 31, and 32. New claims 78-98 are also supported by the specification at page 2, lines 1-3; page 6, line 4; page 14, lines 21-25; and page 18, lines 23-27.

Non-Statutory Double Patenting Rejection

Claims 1-3, 11-16, 17-20, and 33-49 are rejected for obviousness-type double patenting over claims 1-33 of U.S. Patent No. 5,581,998. Claims 21, 22, 28-32, and 51-60 are rejected for obviousness-type double patenting over claims 1-20 of U.S. Patent No. 5,506,203. To obviate the double patenting rejections, the common assignee of record for this application and the two cited U.S. patents has executed the enclosed Terminal Disclaimer (Appendix B) under 37 C.F.R. §§ 3.73(b) and 1.321(b).

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-22 and 26-60 have been rejected for lacking enablement commensurate with the scope of the claims. Applicants traverse the enablement rejection on the ground that, in light of the specification, one of ordinary skill in the art can readily obtain species other than those disclosed in the specification without undue experimentation.

The basis for the Examiner's rejection appears to rely on several factors. First, the Examiner states that:

> With the sole exception of insulin and the C-peptide of insulin, the specification completely fails to teach how to *use* the plethora of pharmaceutical compositions to treat diseases . . .. The specification provides no written description of any diseases which can be treated by these plethora of claimed polypeptides. (page 5 of the Office Action; emphasis in original)

Second, the Examiner states that:

> The specification lacks any written description of any *in vivo* assay by which one skilled in the art could ascertain effective disease therapy for any of the plethora of pharmaceutical polypeptide compositions claimed. (pages 5 of the Office Action)

And third, the Examiner states that:

> [T]he specification fails to teach that inhalation with the instant pharmaceutical compositions can effectively achieve dosages which have been demonstrated to be therapeutic. . . . [T]he skilled artisan would be forced to independently develop assays for testing effective dosages for treatment . . .. (page 6 of the Office Action)

Thus, in summary, the Examiner's position appears to be that (1) the specification fails to provide a written description of diseases which can be treated with the claimed compositions, other than diabetes; (2) the specification fails to describe in vivo assays for determining whether a particular composition can be used to treat a specific disease; and (3) the specification fails to describe assays for determining effective dosages.

In regards to the Examiner's first contention, applicants note that none of the claims specifies the treatment

of a specific disease. Applicants have discovered compositions that result in enhanced absorption of a polypeptide drug in the lower respiratory tract. To illustrate why the rejection is not justified, applicants point out that the compositions and methods of the invention can be analogized to a novel type of syringe and use thereof to deliver pharmaceuticals. The syringe would work as a means to deliver any drug, and so could be broadly claimed for use with any drug. It would be ludicrous to deny such claims just because the applicant did not list diseases, drugs, dosages, and treatment regimens in the application. Similar standards should apply here, where applicant claims compositions, devices, and methods for delivering polypeptide drugs.

Plainly, one skilled in the art would realize that the specific polypeptides recited in the specification and the claims are inherently useful in treating specific diseases or conditions. For example, the 1991 Physicians' Desk Reference (PDR; Appendix C) lists several polypeptide formulations for use in treating specific diseases or conditions. At pages 1970-1971, the PDR describes Syntocinon®, an oxytocin formulation for promoting milk ejection. At pages 1232-1233, the PDR describes the use of glucagon in the treatment of hypoglycemia. At page 1689, the PDR describes Pitressin®, a vasopressin formulation to be used as an antidiuretic whenever water reabsorption is clinically beneficial. These descriptions clearly illustrate that the specification need not describe for which diseases or conditions each listed polypeptide is useful because such utilities are well known in the art.

Consistent with applicants' position is the Examiner's own statement: "The single working example of an *in vivo* assay is the measurement of glucose levels, an assay which is specific for **diabetes** and insulin." (page 5 of the Office Action; emphasis added.) Given that the term "diabetes" does not appear in the specification, the Examiner apparently relied upon general knowledge to conclude (correctly) that insulin can be used to treat diabetes. Certainly, she would agree that one skilled in the art knew that insulin can be used to treat diabetes. Similarly, one skilled in the art would know of conditions that can be treated with other pharmaceutically active polypeptides, including but not limited to those polypeptides listed in the specification.

Turning to the Examiner's second and third contentions, namely that the specification does not provide *in vivo* assays for determining whether and at what dosage the compositions and methods of the invention can be used to treat any disease, applicants note that techniques for *in vivo* testing of pharmaceutically active polypeptides are well known in the art. As examples of such *in vivo* assays, applicants provide in Appendices D through G references describing efficacy testing of growth hormone in bone repair (Carpenter et al., J. Bone Joint Surg. 74-A:359-367, 1992; Appendix D), vasopressin in liver metastasis (Hemingway et al., Br. J. Cancer 64:212-214, 1991; Appendix E), atrial natriuretic factor in acute renal failure (Pollock et al., Renal Failure 14:141-146, 1992; Appendix F), and oxytocin in eating behavior (Arletti et al., Physiol. Behav.

48:825-830, 1990; Appendix G). Although these references do not teach the delivery of polypeptides by inhalation, the experiments described therein can be modified readily according to Examples 3 and 4 on pages 23-25 of the specification so that the polypeptide is administered by inhalation instead of via the routes described in the publications. Once so modified, these methods can be used to determine the effective dosages necessary to achieve a particular pharmacological effect by simply testing a range of dosages in the assay. Because such tests are routine for one of ordinary skill in the art who has read the specification, there is no need for applicants to describe them in the specification.

Applicants therefore submit that one skilled in the art is fully enabled to test the claimed invention for treatment of known diseases or conditions without undue experimentation.

In further support of enablement, applicants submit herewith a copy of PCT application WO 96/19206 (Appendix H). This patent application describes sodium taurocholate-mediated enhancement of absorption of human parathyroid hormone in the lungs of beagle dogs, thereby providing yet another working example and indicating the operability of the present invention.

Rejections under 35 U.S.C. § 102

Illum, U.S. Patent No. 5,707,604.

Claims 1-13, 17-20, 31-44, 48, and 49 are rejected under 35 U.S.C. § 102(e) as anticipated by Illum. Dry powder inhaler device claims 17-20 and 33-49 have been replaced by new claims 78-97.

Applicants traverse on the ground that Illum does not teach or suggest the presently claimed invention: a non-hygroscopic composition (claims 1-13, 31, and 32, as amended), an inhaler device adapted for inhalation through the mouth (new claims 78-98), and a composition having carrier particles of at least 20 microns in diameter so as to form an ordered mixture as defined at page 3, lines 9-14 of applicants' specification (new claims 61-77).

Illum describes bioadhesive microspheres that "will gel in contact with the mucosal surface" (col. 3, lines 26-27). Any material that gels in contact with a moist surface, such as a mucous membrane, does so by absorbing water from the surface. Such a material is therefore characterized as "hygroscopic." In this regard, applicants note that *Webster's New Collegiate Dictionary*[1] defines "hygroscopic" as "readily taking up and retaining moisture."

In contrast, amended claim 1 and new claims 98-100 require that the composition be "in a form of a non-hygroscopic dry powder". The compositions of the invention should not be hygroscopic because any absorption of water by the particles of the composition would result in clumping together and sticking to the container sidewalls, thereby reducing accessibility to the lung. See page 14, lines 25-32, and page 2, lines 5-9, of the specification. Absorption of water by Illum's particles is not a problem because Illum is interested in depositing his particles

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[1]Woolf et al., eds., G. & C. Merriam Co., Springfield, Massachusetts, 1981, p. 557.

in the nose, where larger particles are trapped during inhalation. In fact, the ability to absorb water readily is essential to Illum's teachings. Therefore, these claims are not anticipated by Illum. Since claims 1-13, 31, and 32 all depend directly or indirectly on claim 1, these claims are also not anticipated by Illum.

Nor are the present device claims anticipated by Illum. The only inhaler devices or delivery methods described in Illum require inhalation through the nose (col. 1, line 48, to col. 2, lines 17; col. 2, lines 28-30; col. 8, lines 24-38; col. 8, lines 52-66; and col. 9, lines 34-35). This is so because Illum's contribution to the art is clearly directed to using the nasal mucosa as a novel route of delivery for high molecular weight drugs (col. 1, lines 48-65).

In contrast, new independent claim 78 requires that the dry powder inhaler device be "adapted for inhalation through the mouth," for example, by the inclusion of a mouthpiece. Thus, Illum does not describe the inhaler device of new claim 78. As claim 78 is not anticipated, neither are new claims 79-98, all of which depend directly or indirectly on claim 78.

Illum also fails to describe the pharmaceutical composition of new independent claim 61, which requires the presence of carrier particles having a diameter of at least 20 microns so that an ordered mixture is formed between the particles of active compounds and those of the carrier. Illum does not describe any kind of particles at least 20 microns in size, let alone an ordered mixture of (a) carrier particles

greater than 20 microns in size and (b) active ingredient particles less than 10 microns in size. Therefore, Illum does not anticipate new claim 61, nor claims 62-77, all of which depend directly or indirectly on claim 61.

Durrani, WO 91/16882.

Claims 1, 3-12, 17, 19-21, 26-28, 34-43, and 50-56 are rejected under 35 U.S.C. § 102(b) as anticipated by Durrani. Claims 17-20 and 33-49 have been replaced by new claims 78-97.

Contrary to the Examiner's assertion, Durrani does not describe a phospholipid capable of enhancing the absorption of a polypeptide in the lower respiratory tract, as is required by all pending claims. Durrani's phospholipids are used in the preparation of liposome-drug formulations. On page 9, lines 1-3, Durrani states: "The only requirement for lipid components to be used in the method of the present invention is that the lipids are able to form membranes in aqueous solutions." The phospholipids described in Table 1 of the reference are diacyl phospholipids having fatty acid chains of longer than 12 carbon atoms, likely because monoacyl phospholipids and shorter chain diacyl phospholipids do not generally form liposomes. In contrast, applicants teach that diacyl phospholipids having acyl groups longer than 8 to 10 carbon atoms in length do not enhance absorption of a polypeptide. As applicants' specification points out, this may be due to the lower water-solubility of longer chain diacyl phospholipids (page 11, lines 20-30).

In addition, applicants submit herewith the Declaration of co-inventor Kjell Bäckström under 37 C.F.R. § 1.132 ("the

Bäckström Declaration"; Appendix I). Paragraph 9 of the Bäckström Declaration presents the results of further studies by Dr. Bäckström, which verify that diacyl phospholipids having acyl groups with 10 or more carbon atoms do not enhance absorption of a polypeptide in the lower respiratory tract and thus are excluded from the claims by the funtional limitation requiring such enhancement. Since Durrani does not teach compositions containing phospholipids which enhance absorption of polypeptides through the lower respiratory tract, none of the claims are anticipated by Durrani.

Schipper, Pharm. Res. 10:682-686, 1993.

Claims 1, 3-12, 17, 21, 26, 27, 34-43, and 50-56 are rejected under 35 U.S.C. § 102(b) as anticipated by Schipper. Claims 17-21 and 33-49 have been replaced by new claims 78-97.

Applicants traverse this rejection on the ground that Schipper does not teach or suggest a dry powder composition where at least 50% of the particles of active compounds are 10 μm or less in diameter, as required by all pending claims.

Schipper describes a freeze-dried powder composition containing insulin and dimethyl-ß-cyclodextrin (page 682, second column, last paragraph). As stated in the Bäckström Declaration at paragraph 11, freeze-drying the Schipper formulation would result in relatively large particles, which is consistent with Schipper's intended use of the formulation for nasal administration. As discussed above in regard to the Illum reference, using particles less than 10 microns in diameter maximizes deposition in the lungs, while larger size particles

are preferentially deposited in the upper respiratory tract. Schipper does not describe or suggest a powder composition where at least 50% of the total mass of active compounds are particles of 10 microns or less, as is required by all of the pending claims. Therefore, the pending claims are patentable over Schipper.

CONCLUSION

Applicant submits that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a check in payment of the excess claims fees required by the above amendments and a Petition for Automatic Extension with the required fee.

Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Oct. 28, 1998

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